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Technetium-99m-tetrofosmin in diagnosis of breast cancer and axillary lymph node involvement

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Abstract

BACKGROUND: The aim of this study was to evaluate the accuracy of breast cancer seeking agent Tc-99m-Tetrofosmin in the detection of breast malignancy and axillary lymph node metastases.
MATERIAL AND METHODS: Twenty-eight female patients (mean age 52.4) with 30 breast lesions suspected of malignancy were enrolled in the study. All the patients underwent clinical investigation, Tc-99m Tetrofosmin scintimammography (SMM), mammography (MM) and biopsy/surgery for final histopathologic diagnosis. Patients were injected intravenously with 555 MBq of Tc-99m Tetrofosmin, cubitally, in the contralateral arm to the side of suspicious lesion. Seven minute static scans or at least 2.0 million counts were obtained using single head gamma camera (Orbiter 75, Siemens). Planar images were acquired in left and right prone lateral view as well as in the supine position for an anterior view of chest and axillary region.
RESULTS: SMM scans of 30 breast lesions were compared to the definitive histopathology findings (HP) using decision matrix. In the group of 23 patients with positive SMM scans 19 had breast malignancy: 15 infiltrating ductal cancer, three patients with one infiltrating lobular, one papillary, one colloidal cancer and one patient with cystosarcoma phyllodes-malignant type. SMM detected primary breast malignancy with 95% sensitivity, 60% specificity and 83% accuracy. Axillary dissection was performed in 19/20 with malignant disease. The number of lymph nodes extracted and HP evaluated varied from 4 to 23 per patient. Metastatic involvement was confirmed by HP in 9 out of 20 patients. SMM detected axillary metastases with 55% sensitivity and 80% accuracy.
CONCLUSION: Our results showed that SMM might be useful as a complementary test to improve the sensitivity and specificity of conventional imaging modalities, although SMM in the staging of breast carcinoma was less reliable. Further studies to evaluate the role of SMM in metastatic node involvement are necessary.
Key words: scintimammography, Tc-99m tetrofosmin, breast cancer

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Introduction

Breast cancer is the most frequent malignant disease in women and the leading cause of surgery, chemotherapy and x-ray therapy performed. Pre-treatment evaluation of breast cancer patients should determine the clinical stage of the disease, including the size of the primary tumour, the presence of chest wall invasion and the presence or absence of regional or distant metastases [1].

Availability and extensive use of mammography (MM) have resulted in earlier diagnosis and reduction in the relative risk of death due to breast cancer [2]. Despite the major advantages associated with the use of mammography, this technique has certain limitations in clinical practice. Sensitivity, specificity and accuracy of MM for the population of patients with dense breasts, history of breast surgery and breast implants have been documented as being lower [3]. These patients often require additional imaging for diagnosis [4]. Ultrasound (US) is inexpensive and widely available, useful in differentiating cysts from solid mass, but still insufficient to differentiate benign from malignant lesions [5, 6]. Consequently, a significant number of surgical biopsies based on abnormal mammograms are performed on benign lesions, exposing the patients to the morbidity risk and costs associated with surgery.

Among the additional imaging techniques used to improve the sensitivity and specificity in breast cancer detection, magnetic resonance (MR) imaging and scintimammography (SMM) have yielded good results. MR is useful in women with questionable findings of other breast imaging studies, preoperative evaluation of axillary node involvement and chest wall invasion [7, 8].

Over the last decade, increasing interest in the development of nuclear medicine breast imaging methods has been evident. The majority of studies have been performed using Tc-99m methoxyisobutyl isonitrile (MIBI) or tetrofosmin, cationic complexes which were developed for myocardial perfusion studies. The overall results were encouraging with sensitivity in detection of palpable breast cancer lesions over 90% [9–12], specificity between 72% [9] and 100% [10] and NPV between 88% and 94% offering the possibility to reduce the number of unnecessary biopsies by 34% [11]. For non-palpable lesions 60% sensitivity, 75% specificity, 60% PPV and 75% NPV were reported [12].

Axillary lymph node assessment can be seen in a positive light under the two main aspects, detecting the real axillary lymph node status for therapy planning and, on the other hand, avoiding unnecessary extensive regional lymphadenectomy with possible complications in patients with no regional metastases. Major complications such as thrombosis or injury of axillary veins are infrequent. Minor complications such as oedema of the arm and breast and shoulder dysfunction are more common. With the general recognition that axillary dissection was principally a prognostic rather than therapeutic procedure, great efforts were made to asses whether the lymph nodes were positive or negative using non-invasive methods. Mammography rarely provides a satisfactory projection for the evaluation of axillary regions yielding in sensitivity in detection of axillary lymph node metastases about 40% [13]. Axillary lymph nodes can be demonstrated by ultrasonography, without the ability to distinguish the lymph node enlargement due to the inflammation from this caused by metastatic involvement [14, 15]. As an alternative, the sentinel lymph node concept has been developed for tumour staging and for subsequent related further surgical strategies. Although a considerable number of articles were devoted to scintimammography in breast cancer detection, only a few studies evaluated the usefulness of SMM in diagnosis of metastatic lymph node involvement.

The aim of this study was to asses, in our own environment, the usefulness of Tc-99m-Tetrofosmin scintimammography in diagnosis of breast cancer and axillary metastatic involvement.

Material and methods

Twenty eight female patients (mean age 52.4) with 30 breast lesions suspected of malignancy were included in the study. In all patients, clinical investigation, mammography and biopsy or surgery for final pathological finding were performed.

Scintimammography was performed with Gamma camera (Orbiter 75, Siemens, Erlangen, Germany) equipped with low energy high-resolution collimator. Tc-99m-Tetrofosmin dose activity of 555 MBq was injected intravenously cubitally, in the arm contralateral to the side of suspicious lesion. Planar imaging was performed using 128 × 128 matrix with acquisition time of 7 minutes. Patients were examined in left and right prone lateral view, as well as in the supine position with the hands raised above the head for an anterior view of the chest and axillary region. Scintiscans were evaluated as negative (–), equivocal (+), probably positive (++), or definitely positive (+++).

Scintimammography scans and mammograms of 30 breast lesions were compared to the definitive histopathological findings using a decision matrix, and the results expressed as: sensitivity, specificity, accuracy, positive (PPV) and negative predictive value (NPV). Nineteen patients underwent axillary lymph node dissection. Scans of axilla were concluded as positive or negative and then correlated with the final histopathological findings.

In all patients, mammography of both breasts was done in cranio-caudal and lateral directions. Mammograms were evaluated as positive when the direct signs (mass of high radiographic density, microcalcifications) or indirect signs (architectural distortion, parenchymal asymmetry, prominent duct etc.) were presented.

Results

In the entire group of patients lesion size ranged from 6 to 70 mm. In 10 lesions histopathologic findings were benign revealing fibrocystic dysplasia in five cases, fibroadenoma in four cases and granuloma in one patient (Table 1). Lesion size ranged from 20 to 70 mm. Among 30 histologically diagnosed lesions, 20 were malignant: 14 infiltrating ductal (ID), one case of intraductal carcinoma, two infiltrating lobular (IL), one papillary, one colloid carcinoma and one tumour phyllodes-malignant type, ranging from 6 to 50 mm (Table 2). Tc-99m-Tetrofosmin SMM was true positive in 19/20 patients with malignant disease. One false negative result was obtained in 20 mm ID carcinoma. Scintiscans were

Table 1. Scintimammography, mammography and histopathology in benign lesions

Patient No	SMM	MM	Diameter [cm]	PH
1.	++	+	4.5	Fibroadenoma microcystic with metaplasio
2.	–	+	–	Fibrocystic dysplasia
3.	++		2.7	Fibroadenoma
4.	+	+	–	Granuloma foreign body and lipogranuloma
5.	–	–	–	Dysplasio fibroadenotic micro and macro cystic proliferative
6. r	–	–	–	Fibrocystis dysplasia
7. l	–	–	–	Fibrocystis dysplasia
8.	–	–	2.0	Fibroadenoma
9.	–	–	–	Fibrosis
10.	+++	–	7.0	Fibroadenoma

Table 2. Scintimammography, mammography and histopathology in malignant lesions

Patient No	SMM	MM	Diameterr (cm)	PH
1.	++	+	3.5	Intraductal carcinoma with central necrosis and infiltrating multicentric ductal carcinoma
2.	+	+	0.6	Infiltrating ductal carcinoma
3.	+++	+	1.7	Infiltrating ductal carcinoma with central necrosis et microcalcifications
4.	++	+	5.0	Cystosarcoma phylodes (malignant type)
5	+++	–	2.8	Infiltrating ductal carcinoma
6.	+++	+	2.8	Colloid carcinoma
7.	+++	+	3.0	Infiltrating ductal carcinoma
8.	+++	+	2.0	Infiltrating lobular carcinoma multicentric
9.	++	+	1.5	Infiltrating ductal carcinoma
10.	++	+	2.1	Infiltrating ductal carcinoma with central necrosis
11.	+++	+	1.7	Infiltrating ductal carcinoma
12	+++	+	2.8	Ductal carcinoma
13.	+++	+	1.9	Infiltrating ductal carcinoma
14.	+++	+	2.4	Infiltrating ductal carcinoma
15.	+	–	2.0	Infiltrating ductal carcinoma
16.	+++	+	1.6	Infiltrating ductal carcinoma multicentric
17.	++	+	2.0	Infiltrating ductal carcinoma
18.	++	–	1.1	Papillary intraductal carcinoma
19.	+++	+	2.2	Infiltrating ductal carcinoma
20.	–	–	1.0	Infiltrating lobular carcinoma multicentric

Table 3. Histopathology and Tetrofosmin axillary uptake in 19 patients with malignant breast disease and axillary resection

Patient No	Total no of lymph node examined	No of lymph node affected	Tetrofosmin axillary uptake
1.	12	1	+
2.	9	0	–
3.	7	0	–
4.	10	0	–
5.	14	3	+
6.	8	0	–
7.	17	1	–
8.	12	0	–
9.	15	6	+
10.	14	9	+
11.	8	0	–
12.	13	0	–
13.	5	0	–
14.	14	5	–
15.	24	14	–
16.	4	1	+
17.	6	0	–
18.	12	0	–
19.	6	2	–

true negative in 6 out of 10 cases, 4 false positive results were obtained in 3 fibroadenomas bigger than 20 mm and in one case of lipogranuloma. Sensitivity of SMM was 95%, specificity 60%, accuracy 83%, PPV 83% and NPV 85%.

Among 20 cases of malignancy, MM was positive in 16 cases. Four false negative results were obtained (two ID, one IL and one case of papillary carcinoma) MM was true negative in 7/10 HP confirmed benign lesions, and false positive in 3 cases. The overall sensitivity of MM in detecting the malignant lesion was 80%, specificity 70%, accuracy 79%, PPV 84% and NPV 70%.

Nineteen patients with malignant breast disease (except one patient with cyst sarcoma phyllodes), underwent axillary lymph node dissection revealing metastases in 9 of them. The number of lymph nodes examined by histopathology varied from 4 to 23 (Table 3). Increased tracer uptake in axilla was obtained in

5 patients, yielding 55% sensitivity of SMM in detecting lymph node metastastases. No false positive results were found.

Discussion

Among the additional techniques used to improve the sensitivity and specificity in detecting breast cancer, SMM using either Tc-99m methoxyisobutyl isonitrile (MIBI) or Tc-99m-Tetrofosmin has been a useful tool in imaging malignant lesions.

Tetrofosmin is a lipophilic cation and the exact mechanism of its cellular uptake by cancer cells is still under investigation. Based on the structural analogies with MIBI, Tetrofosmin was thought to passively diffuse through membranes in response to transmembrane potentials and its accumulation in mitochondria was probably due to an active storage process. Compared to Tc-99m MIBI, Tc-99m Tetrofosmin shows similar heart uptake, retention and blood clearance kinetics, but significantly faster clearance from liver and lung, offering the possibility of higher quality images due to the higher "tumour-background" ratio [16].

In the last decade numerous studies have shown good results of SMM in the evaluation of patients with suspected breast cancer, particularly in identifying the presence and site of cancer.

Lind and co-authors reported sensitivity of 91% and specificity of 74% for Tc-99m-Tetrofosmine SMM [9], while Mansi and his group detected malignant breast lesions with 92% sensitivity, 100 % specificity and 95% accuracy, and Clinical trials carried out with Tc-99m MIBI obtained quite satisfactory results in the identification of primary breast cancer with 87% sensitivity and 65% specificity [17]. SMM was also shown to be more accurate than MM in diagnosis of recurrent breast cancer [18]. In our patients, in accordance with previous studies [19], SMM in diagnosis of primary malignancies showed high sensitivity of 92%. One false negative scan was obtained in a patient with a 20 mm ID carcinoma. Considering the pattern of abnormal findings, 12/19 breast cancer lesions were presented as the „hot spot" (Figure 1). The smallest lesion measured only 6 mm (ID), and the biggest one had a 50 mm diameter: cyst sarcoma phyllodes–malignant type (Figure 2).

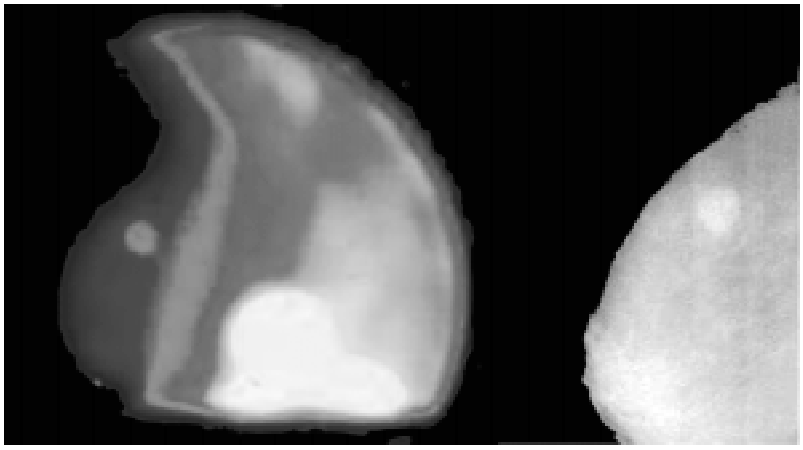

Figure 1. 65-year-old female with a palpable mass in the upper and outer quadrant of her left breast. Scintimammography (left) showed an intense area of tracer uptake corresponding to clinical and mammographic findings. (right) HP evaluation revealed infiltrating ductal carcinoma.

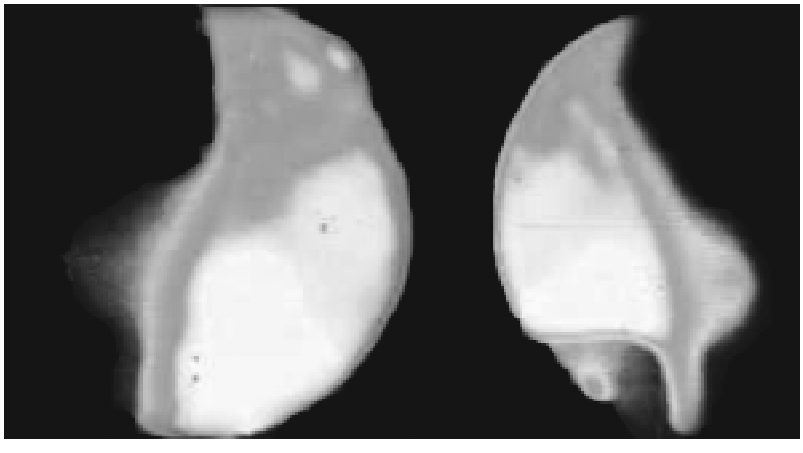

Figure 2. SMM, lateral views in prone position showing tracer activity in the right breast uptake in 50 mm Cystosarcoma phyllodes malignant type.

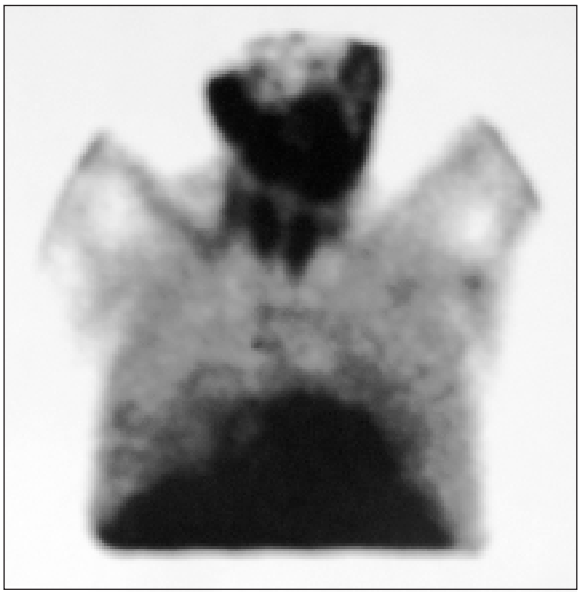

Figure 3. SMM, Anterior chest view demonstrating small focus of tracer activity in upper outer quadrant of the left breast and clearly increased uptake in ipsilateral axillary region. HP revealed ID carcinoma with central necrosis and metastases in 6/15 lymph nodes examined.

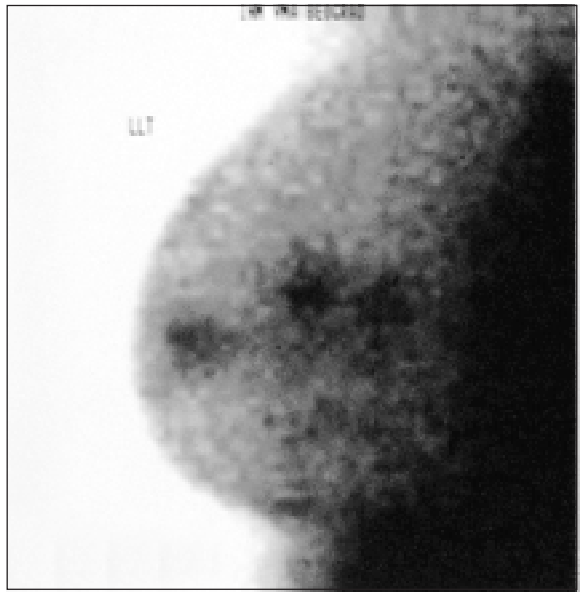

Figure 4. 47-year-old female with palpable mass in upper outer quadrant of left breast. MM demonstrated one area suspected of malignancy. SMM showed multiple foci of increased tracer activity. PH revealed multicentric infiltrating lobular carcinoma.

Necrotic change in tumour centre is one of biological factors affecting the tracer uptake. This observation was done by authors focused on basic approach of radioimmunoscintigraphy [20]. The relationship between tumour size and uptake is not linear because the larger the tumour is, proportionally the greater are the stromal and cystic and necrotic changes. Infiltrating lesions with central necrosis at SMM were presented as the in homogenously and moderately increased tracer uptake by tumours enabling the visualization of metastatic lymph node involvement (Figure 3).

Breast cancer is very commonly multifocal, but rarely multicentric, thus referring to the independent foci of cancer not in relation to the primary tumour. SMM was found to identify more cases of multifocal and multicentric cancer than MM and/or US (52% *vs.* 22%) [21]. Scans of patient No 19 (Table 2) showed multiple foci of the increased tracer activity. Histopathology revealed multicentric infiltrating ductal carcinoma (Figure 4).

The case of a patient No 15, with nipple secretion and cytology positive for malignant cells in nipple expiration, was most interesting. Standard procedures such as mammography and US were not able to detect anything suggesting malignant abnormality. Tc-99m Tetrofosmin SMM revealed the filamentous area of increased uptake in the left breast. HP confirmed ID carcinoma expanded through the larger ducts, with no defined mass. In this case SMM was the only imaging method suggesting breast malignancy.

In our study SMM showed a higher overall sensitivity in comparison with MM (95% *vs.* 80%). At SMM 19/20 cancers were detected while MM „missed" four cancer lesions.

The median size of extirpated cancer in our patients was 23 mm (6–50). Scans evaluated as „definitely positive" were related to tumour size of at least 20 mm. In 3 cases with lesion diameter between 10 and 20 mm, SMM was evaluated as probably positive, and in the case of 6 mm malignant lesion SMM was equivocal. Further investigations are necessary, but the tumour size seems to be an important factor in determining the scintigraphic findings. In our experience, a malignant lesion size of nearly 20 mm was most convenient for Tc-99m Tetrofosmin imaging. This observation is concordant with the results reported by Cwikla et al. Comparing the diagnostic accuracy of SMM and MM in groups of different size lesions, SMM was shown to be more sensitive in all groups, and significantly more accurate in tumours below 2.0 cm [22].

Normal scintiscans, characterized by homogenous radiotracer distribution through the breast tissue with no foci of increased activity, were obtained in 6/10 benign breast lesions. In 19 out of 23 patients with positive SMM the breast cancer was revealed, in the others 3 fibroadenomas and one lipogranuloma giving a specificity of 60%. These findings are in contrast to some publications reporting no tracer uptake in benign lesions [23]. On the other hand, Palmedo and other authors reported specificity between 62–75% — quite similar to our results [12]. Three of four falsely positive results in our group were obtained in patients with fibroadenomas larger than 20 mm. Histopathological examination confirmed hypercellularity of the lesions might be the reason for pathological tracer accumulation. Also, the size of fibroadenoma seems to be an important factor.

With general recognition that axillary resection is rather a prognostic than a therapeutic procedure, increasing interest in preoperative axillary node staging is evident. The capability of available radioimaging systems (US, CT and MRI) of detecting lymph nodes enlargement is limited by the spatial resolution of the system. In the meantime, lymph nodes that are normal in size can be involved with metastases. Scintimammography using cationic lipophilic agents has recently been focused on the detection of pri-

mary breast cancer; the data of axillary metastasis evaluation are still limited. Early reports were encouraging; axillary lymph node metastases were detected with 91.6% sensitivity and 92.3% specificity [23]. In a study of diagnosis and staging of breast cancer, Tc-99m MIBI SMM was found to yield true positive results in 7 of 11 cases (64%) of axillary lymph node metastases and true negative in 18 of 20 cases with 81% accuracy [24]. Spanu et al. performed a comparative study between planar Tc-99m-Tetrofosmin SMM and supine SPECT [25]. The results of this study, comprising the largest series of patients reported in literature, demonstrated higher sensitivity for SPECT than for planar imaging in the detection of palpable (100% vs. 82%) and non palpable (92.8 % vs. 35.7%) axillary metastatic nodes.

Positron emission tomography should permit the recognition of involved lymph nodes due to increased metabolic activity of malignant tissue regardless of size, but in practice it is still incapable of detecting micrometastases. An extensive study conducted at the Instituto Nazionale Tumori di Milano reported 92.9% sensitivity and 89.1% accuracy of FDG-PET in patients with no palpable lymph nodes, and 96.7 % sensitivity and 92.1% accuracy in patients with palpable nodes. Other clinical trials carried out with FDG--PET did not obtain similar results. The sensitivity of FDG-PET to detect occult axillary metastases in operable breast cancer was low (25%) with a specificity of 97% [26]. Comparing preoperative PET scans to the histopathological analyses of the sentinel lymph node, sensitivity of FDG-PET to detect metastases was 43% and specificity was 94 % [27]. It was suggestive that FDG-PET should be focused on exploiting its nearly perfect specificity and that in cases with positive lymph node in PET staging, axillary lymph node revision could be performed immediately without other diagnostic procedures. In our group of patients sensitivity of SMM in detecting lymph node metastases was 55%, significantly lower than the sensitivity in detecting the primary breast malignancy. The number of lymph nodes examined by HP varied from 4 to 23. Scintimammographic imaging of axillary lymph node involvement was difficult even when a large number of lymph nodes was affected. We obtained false negative scans with no foci of tracer activity in the region of axilla in patients with metastases in 14 out of 23 nodes removed. In contrast, true positive results were obtained in patients with metastases in only 1 out of 12 lymph nodes examined. The majority of positive Tc-99m Tetrofosmin axillary scans were related to patients with central necrosis in the primary breast tumour. No false positive results were found.

Conclusion

Breast scintigraphy cannot replace conventional methods in the diagnosis of breast cancer patients. Time consuming and more expensive compared to conventional mammography, breast scintigraphy undoubtedly cannot be considered as a screening method. Based on the results obtained in our study we concluded that Tc-99m Tetrofosmin scintimammography could improve the diagnostic accuracy of the other breast imaging modalities. In patients with inconclusive or discordant findings of standard tests, scintimammography might be a useful tool aimed at facilitate the early diagnosis of breast cancer as well as to reduce the number of biopsies performed on benign lesions. Our results suggested that this method could not be considered for staging breast cancer patients.

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